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The Action of Streptomycin and Usnic Acid on the Development of Tuberculosis in Guinea Pigs

By ALFRED MARSHAK, PH. D. and MARVIN KUSCHNER, M. D.*

In 1947, Marshak (1) demonstrated the marked *in vitro* antibacterial action of usnic acid on *M. tuberculosis*, a finding since confirmed by Stoll, Brack, and Renz (2), Barry et al. (3), and Shibata, Ukita, et al. (4). At that time additional experiments in which usnic acid was administered to a relatively small number of guinea pigs infected with human tubercle bacilli seemed to indicate that the drug effected definite retardation of the disease.

The work herein reported was undertaken in order to reexamine the effect of the drug on experimentally induced tuberculosis in a larger number of animals, to compare the efficacy of the drug with that of streptomycin and to test for possible synergistic action in combination with streptomycin.

Methods and Materials

Tubercle bacilli of the strain H₃₇RV were isolated from a guinea pig on Loewenstein's medium, transferred to Dubos medium, then transferred again to Dubos for 10 days, at which time each guinea pig in this study was infected by inoculation with .02 mg. dry weight of this culture.

The animals used were all of the Hartley strain (5, 6). Ninety-nine virgin female guinea pigs were divided into five groups so that each group had a similar weight distribution and a mean weight of approximately 400 grams. The range in weight was 332 to 498 grams. Group I contained 19 guinea pigs; the other four groups contained 20 each.

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Group I, the control group, was untreated.

Group II received 20 mg. of usnic acid in oil-Tween 80 mixture subcutaneously every day for 6 days, then 10 mg. daily for 24 days.

Group III received 3 mg. of streptomycin twice daily for 30 days.

Group IV received 1 mg. of streptomycin twice daily for 30 days.

Group V received 20 mg. of usnic acid in oil-Tween 80 mixture for 6 days, then 10 mg. daily for 24 days. In addition, this group received 2 mg. of streptomycin daily for the 30-day treatment period.

In all groups treatment was started on the day following inoculation with tubercle bacilli and maintained for 30 days. All animals were weighed every 2 or 3 days. All surviving animals were sacrificed 41 to 44 days after inoculation or 11 to 14 days after cessation of treatment. All animals were autopsied, and the lungs, liver and spleen, the organs chosen for assay, were fixed in 10 percent formalin. Gross estimates of the extent and severity of the disease in the lungs and liver were made by counting all nodular lesions seen on the surface of these organs and those seen on multiple cross-section 5 mm. apart in each organ. The number of such lesions, their size and confluency determined the grading of lungs and liver as 0—no disease; 1—minimal disease; 2—slight disease; 3—moderate disease, or 4—marked disease. Because of the difficulty in distinguishing Malpighian corpuscles from focal, nodular tuberculous lesions in the spleen, it was found impracticable to count lesions in that organ. Accordingly, the spleen was graded from 0 to 3, that is, no disease, slight, moderate or marked involvement, depending upon enlargement, capsular thickening, and bulging of obvious lesions through the capsule.

Paraffin sections of the lungs, liver, and spleen of each animal were stained with hematoxylin and eosin and duplicate sections were prepared and stained by the Ziehl-Neelsen method. The organs were then graded again on the basis of microscopic findings. The criteria for grading were size of the lesion, type of cellular reaction, and presence or absence of necrosis. It was found that tubercle bacilli were so rare in all lesions that they could not be taken into account in the grading. On the basis of microscopic findings, all organs were graded 0, 1, 2, 3, or 4.

Results

There were five deaths in the entire group of 99 animals. All five were in group V, the group which received combined streptomycin and usnic acid therapy. These animals died 7, 12, 27, 31 and 34 days after inoculation. None of the five died of tuberculosis. In the animal which died 7 days after inoculation, evidence was found of direct injection of the drug into the peritoneal cavity, but there was no peritonitis. There was no evidence of tuberculosis nor any apparent morphologic lesion to explain the death. The animal which died 12 days after inoculation was found to have an extensive area of

**CUMULATIVE WEEKLY CHANGE FROM INITIAL
MEAN WEIGHT FOR FIVE GROUPS OF GUINEA PIGS**

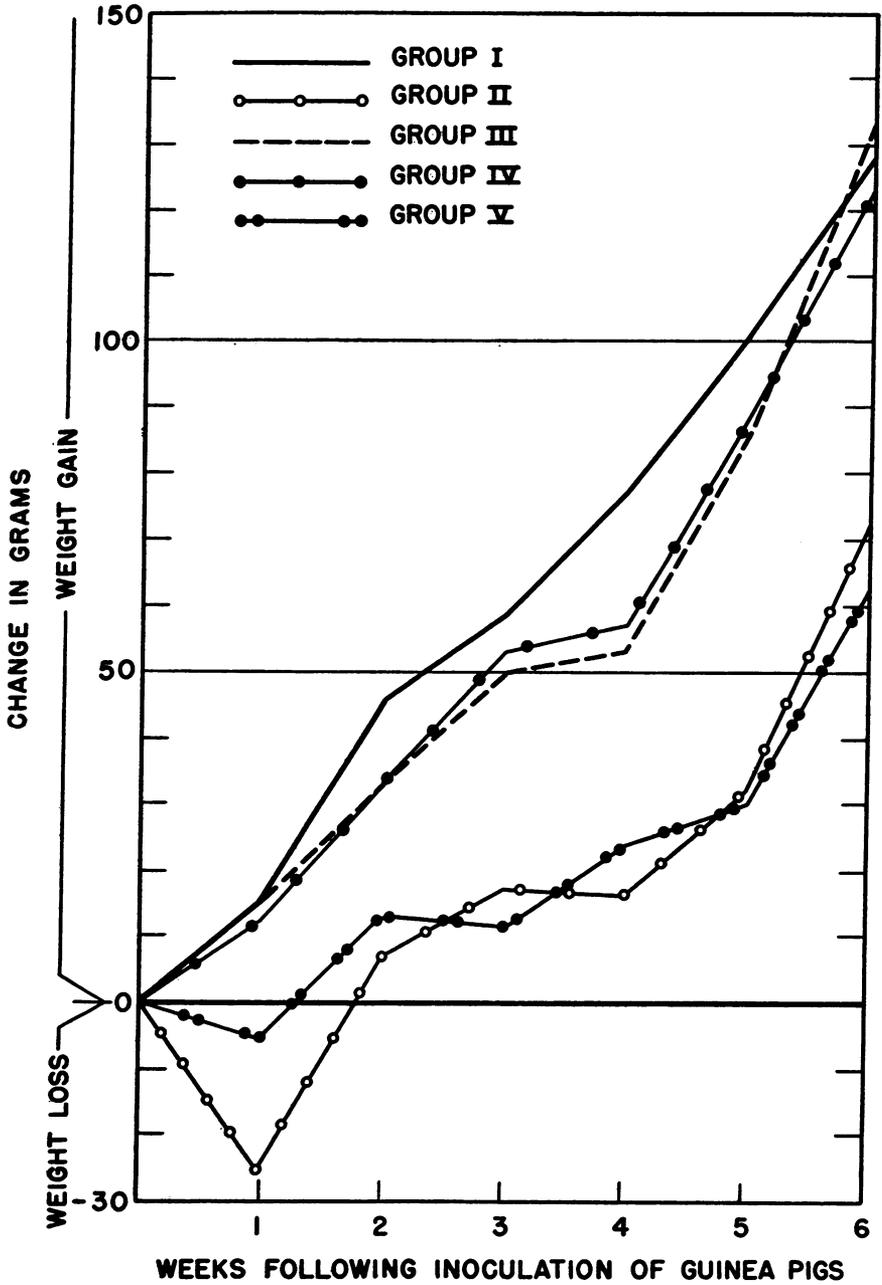


Figure 1.

necrosis in the liver which microscopically resembled an infarct. The possibility of direct injection of the drug into the liver could not be ruled out. Again there was no evidence of tuberculosis. The animal which died 27 days after inoculation had moderate tuberculous lesions in the lungs, liver, and spleen. These were not severe enough to explain the death of the animal; however, no other cause was found. The animals which died 31 and 34 days after inoculation both had extensive acute pneumonia. These animals were cage mates. Both had minimal tuberculous lesions in the liver and spleen. All five animals were excluded from the calculations of variations in mean weights and in the estimations of severity of disease.

Weights. The weekly mean weights for each group and the change between the initial weight and the weight for each succeeding week are presented in table 1, and the change in weight is represented graphically in figure 1. It may be seen that the rates of gain and the final total gain in groups, I, III and IV are fairly comparable. In groups II and V, however, both of which received usnic acid, there was little gain in weight until after the cessation of therapy at the fourth week.

Table 1. *Weekly mean weight and cumulative weekly change from initial mean weight for five groups of guinea pigs*

Group	Initial mean weight	Weekly mean weight (grams)						Cumulative weekly change (grams) from initial mean weight					
		1st week	2d week	3d week	4th week	5th week	6th week	1st week	2d week	3d week	4th week	5th week	6th week
I Control.....	409	424	455	468	486	510	537	+15	+46	+59	+77	+101	+128
II Usnic acid.....	397	372	404	414	413	429	469	-25	+7	+17	+16	+32	+72
III Streptomycin-6 mg./day.....	403	418	436	453	456	489	536	+15	+33	+50	+53	+86	+133
IV Streptomycin-2 mg./day.....	402	414	435	455	459	491	525	+12	+33	+53	+57	+89	+123
V Usnic acid+streptomycin-2 mg./day.....	411	406	424	422	435	441	474	-5	+13	+11	+24	+30	+63

Severity of Disease. Within each group, the gross findings in the liver, spleen and lungs are presented in table 2 according to severity of disease; and represented graphically in figures 2, 3, and 4, respectively. In groups III and V (6 mg. streptomycin daily, and 2 mg. streptomycin plus 10 mg. usnic acid), 85 to 94 percent of the animals had either no evidence of disease in the liver (category 0), or the mildest form (category 1). In striking contrast only 10 to 40 percent of the animals in the other groups fell into severity categories 0 and 1 (fig. 2). Evaluation of gross lesions in the spleen (fig. 3) gave a similar distribution. Although the distribution of lung lesions (fig. 4) in general tends to suggest lesser lesions in groups III and V, these differences are not completely consistent particularly because 31 percent of the animals in group I showed no gross lesions of the lungs.

TUBERCULOSIS ON GROSS EXAMINATION OF LIVER

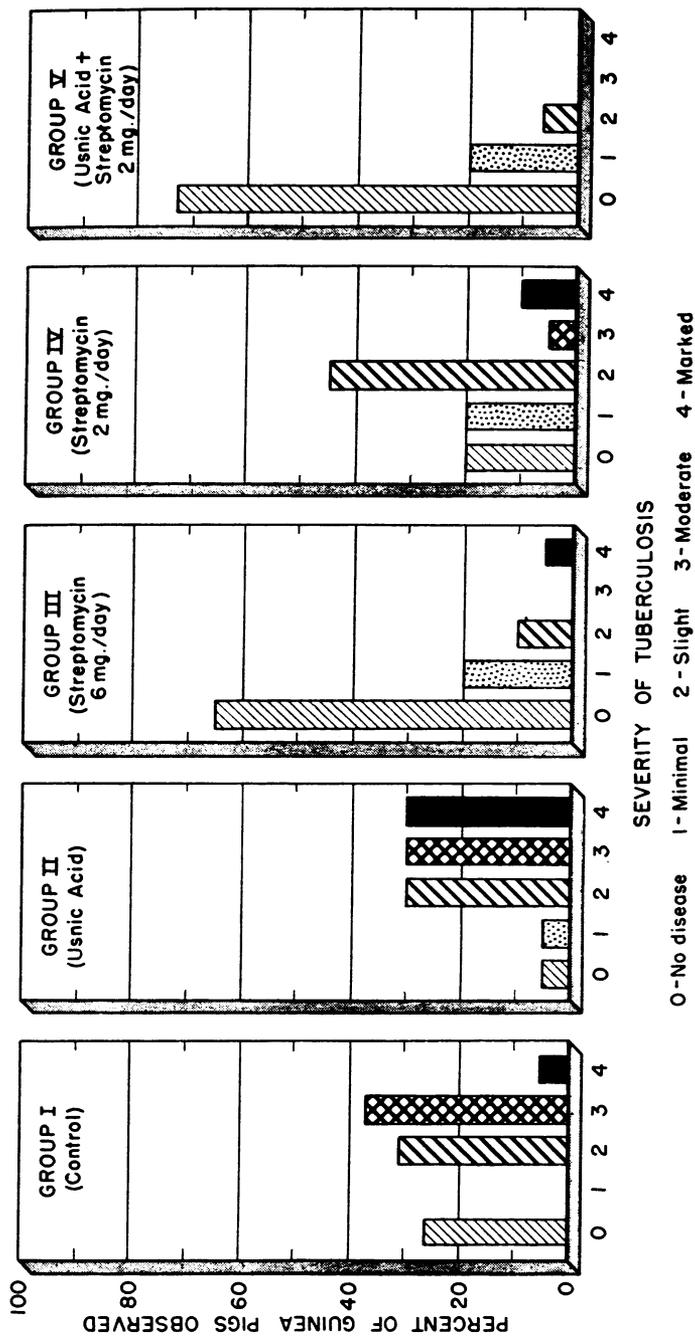


Figure 2.

TUBERCULOSIS ON GROSS EXAMINATION OF SPLEEN

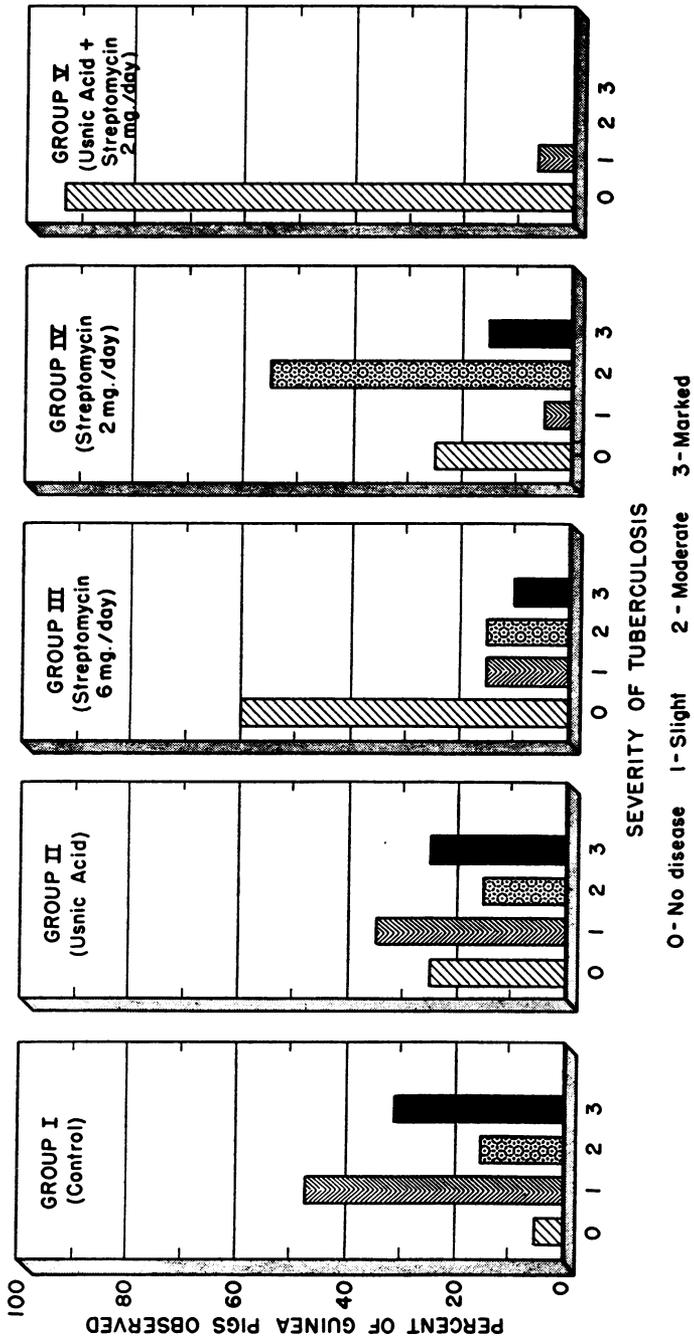


Figure 3.

TUBERCULOSIS ON GROSS EXAMINATION OF LUNGS

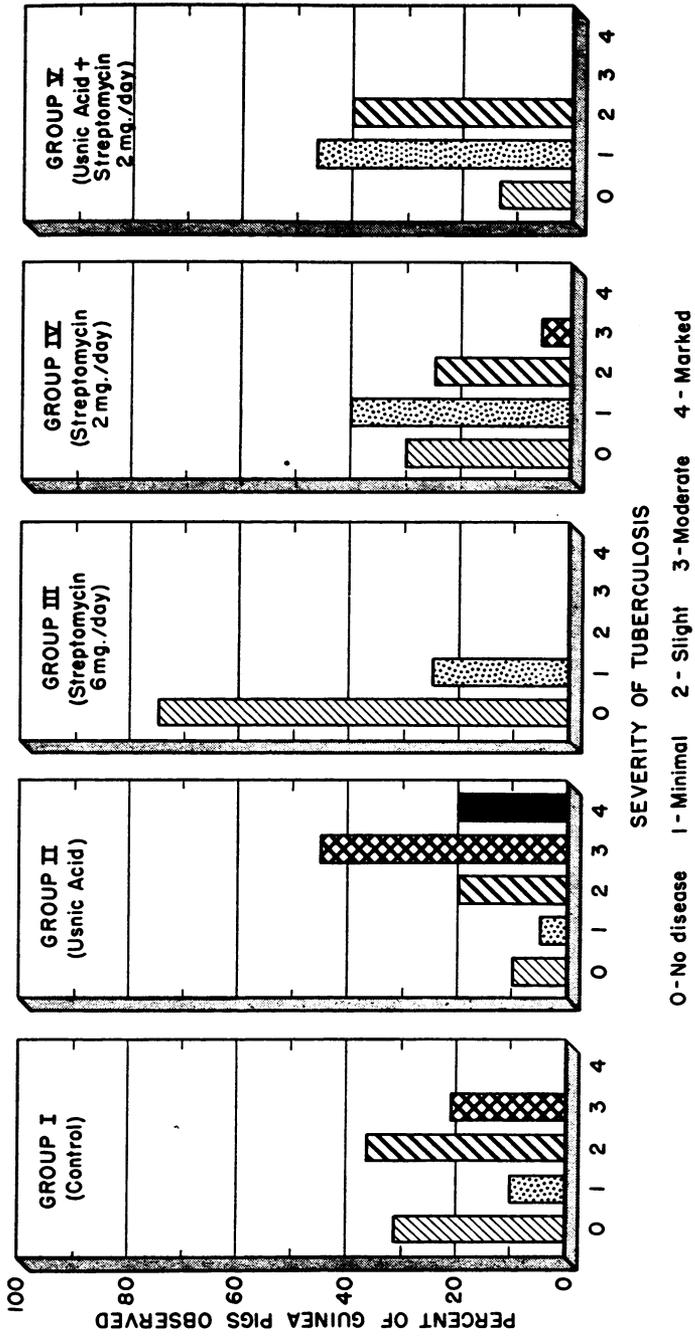


Figure 4.

One of the difficulties here, and this remains true even after microscopic examination, is the tendency to confuse with tuberculous lesions many of the nonspecific infiltrates to which guinea pigs are subject. Because the gross and microscopic lesions of tuberculosis are much more specific and more easily identified in the liver and spleen, we believe that these organs are more useful than the lungs for assaying the severity of disease.

Table 2. *Percent of animals in each group showing tuberculosis according to assigned categories of severity on gross examination of the liver, spleen, and lungs*

Category of severity of tuberculosis	I	II	III	IV	V
	Control	Usnic acid	Streptomycin 6 mg./day	Streptomycin 2 mg./day	Usnic acid +streptomycin
Liver					
0—No disease.....	26.3	5.0	65.0	20.0	73.5
1—Minimal.....	-----	5.0	20.0	20.0	20.0
2—Slight.....	31.5	30.0	10.0	45.0	6.6
3—Moderate.....	36.9	30.0	-----	5.0	-----
4—Marked.....	5.3	30.0	5.0	10.0	-----
Spleen					
0—No disease.....	5.3	25.0	60.0	25.0	93.3
1—Slight.....	47.5	35.0	15.0	5.0	6.6
2—Moderate.....	15.7	15.0	15.0	55.0	-----
3—Marked.....	31.5	25.0	10.0	15.0	-----
Lungs					
0—No disease.....	31.5	10.0	75.0	30.0	13.3
1—Minimal.....	10.6	5.0	25.0	40.0	46.7
2—Slight.....	36.9	20.0	-----	25.0	40.0
3—Moderate.....	21.0	45.0	-----	5.0	-----
4—Marked.....	-----	20.0	-----	-----	-----

Table 3 and figures 5, 6, and 7 give the results of the microscopic grading of lesions. For both the liver (fig. 5) and the spleen (fig. 6) microscopic examination produces observations similar to those obtained by gross inspection. Microscopic examination of the lesions in the liver, for example, discloses that 55 to 73 percent of the animals in groups III and V had either no lesion (category 0) or those of least severity (category 1), while, in the other groups, most of the animals were rated in severity category 2 or higher.

In general, distribution of lesions in the lung (fig. 7) is similar to that seen in the livers and spleens. The 53 percent of animals in group V which showed lung lesions of grades 2 and 3 is not consistent with this general pattern, and here again, as in the gross examination, we believe that the difficulties in accurate diagnosis in this organ introduce an unavoidable error in these estimates.

TUBERCULOSIS ON MICROSCOPIC EXAMINATION OF LIVER

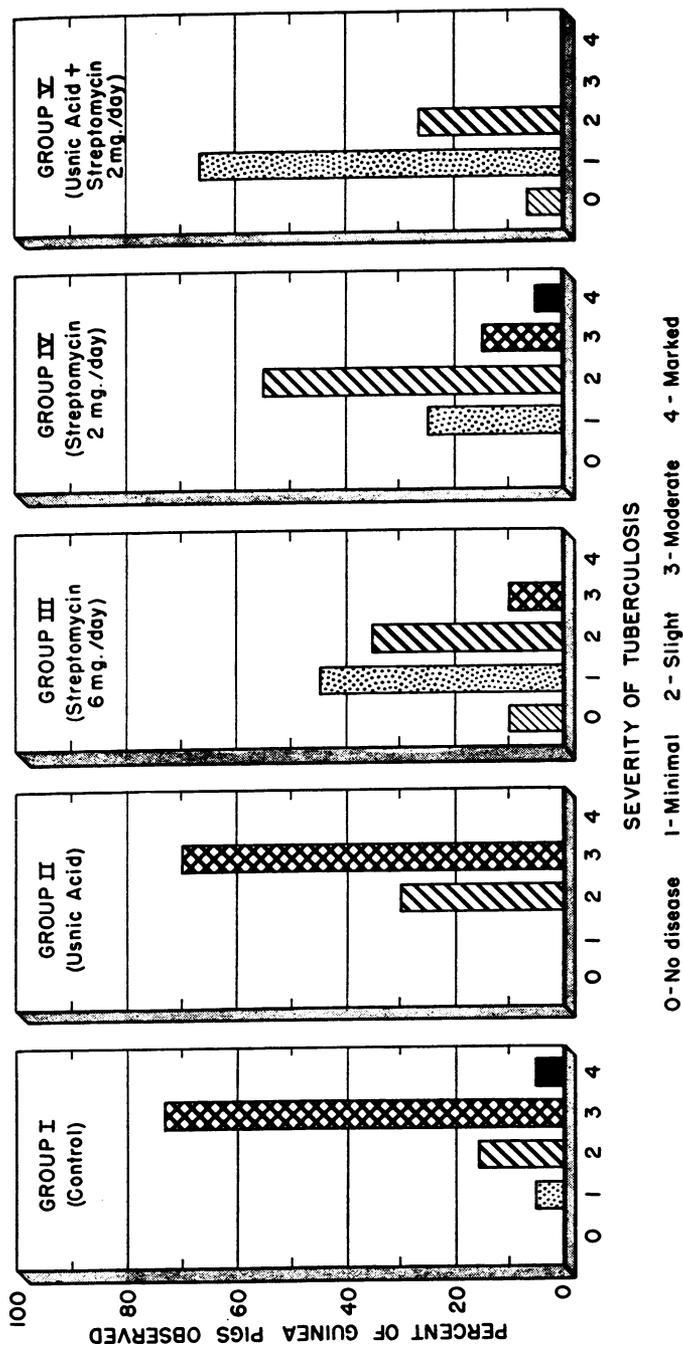


Figure 5.

TUBERCULOSIS ON MICROSCOPIC EXAMINATION OF SPLEEN

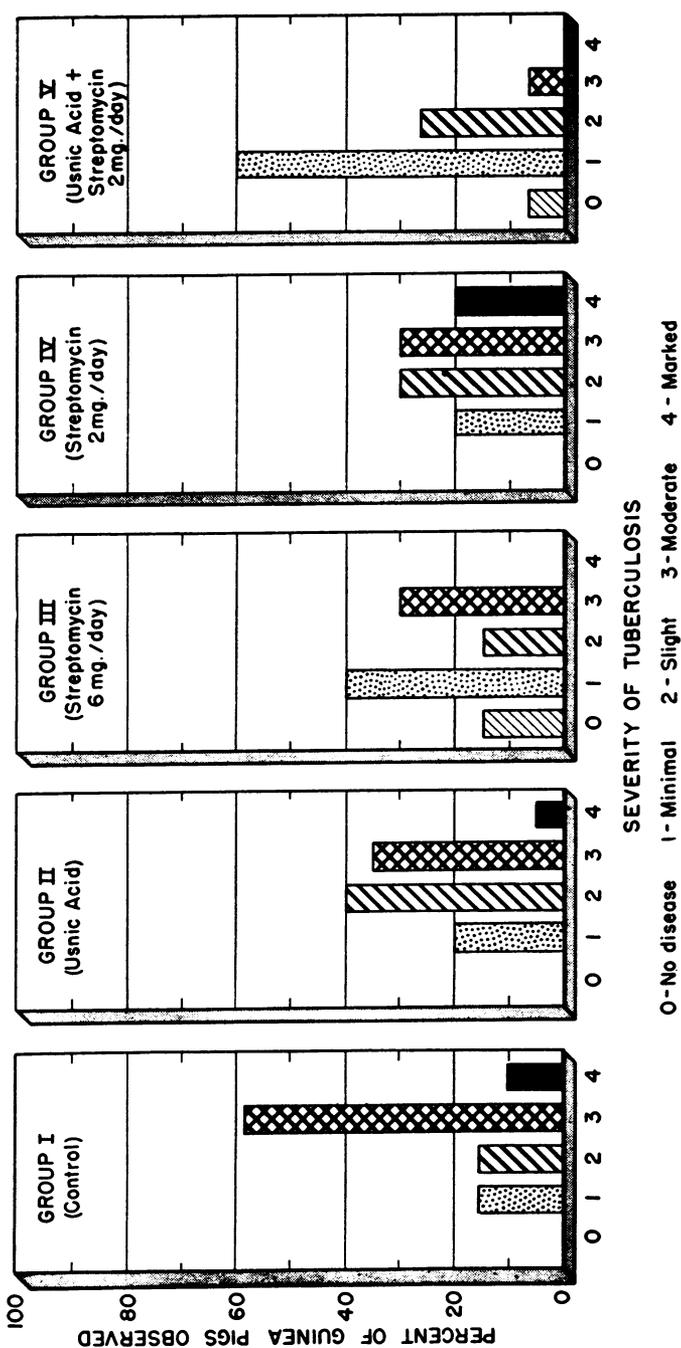


Figure 6.

TUBERCULOSIS ON MICROSCOPIC EXAMINATION OF LUNGS

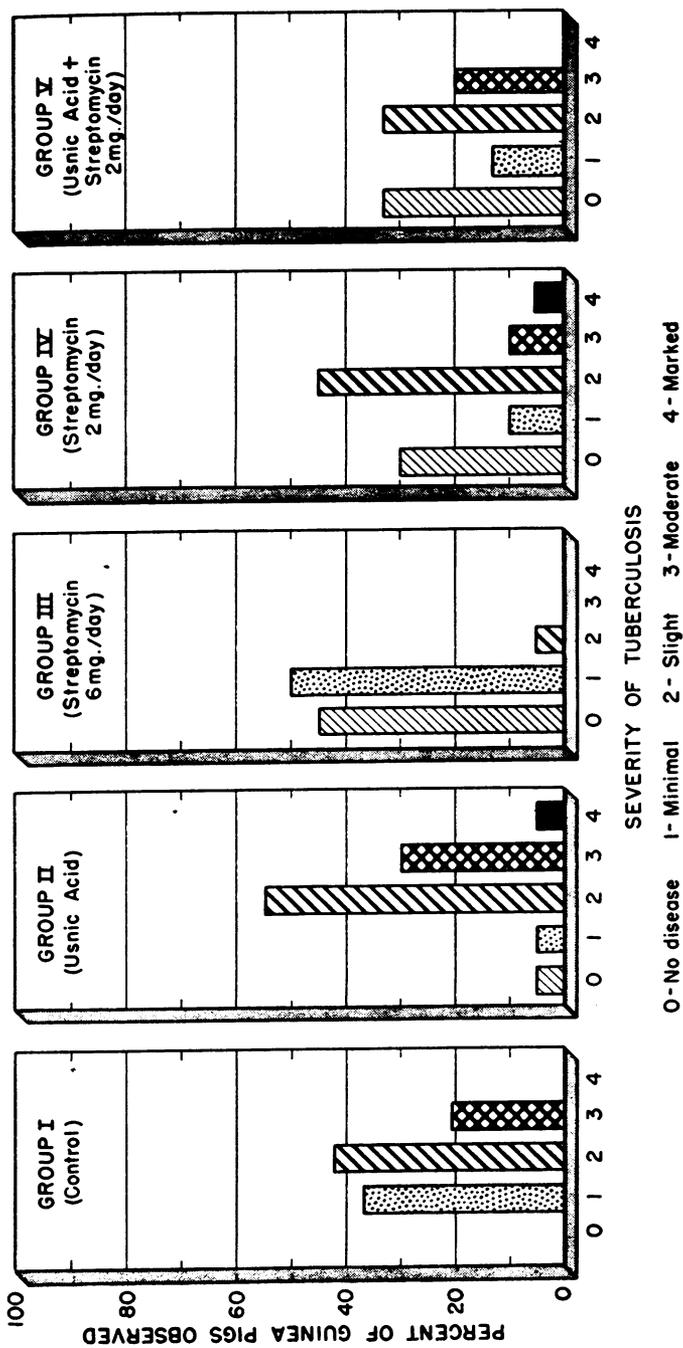


Figure 7.

Table 3. Percent of animals in each group which showed tuberculosis according to assigned categories of severity on microscopic examination of the liver, spleen, and lungs

Category of severity of tuberculosis	I	II	III	IV	V
	Control	Usnic acid	Strepto- mycin 6 mg./day	Strepto- mycin 2 mg./day	Usnic acid + strepto- mycin
Liver					
0—No disease.....			10.0		6.6
1—Minimal.....	5.3		45.0	25.0	66.7
2—Slight.....	15.7	30.0	35.0	55.0	26.7
3—Moderate.....	73.7	70.0	10.0	15.0	
4—Marked.....	5.3			5.0	
Spleen					
0—No disease.....			15.0		6.6
1—Minimal.....	15.7	20.0	40.0	20.0	60.0
2—Slight.....	15.7	40.0	15.0	30.0	26.7
3—Moderate.....	58.0	35.0	30.0	30.0	6.6
4—Marked.....	10.6	5.0		20.0	
Lungs					
0—No disease.....		5.0	45.0	30.0	33.3
1—Minimal.....	36.9	5.0	50.0	10.0	13.4
2—Slight.....	42.1	55.0	5.0	45.0	33.3
3—Moderate.....	21.0	30.0		10.0	20.0
4—Marked.....		5.0		5.0	

Comment

The absence of any deaths from tuberculosis in the 6 weeks following inoculation of a dose of tubercle bacilli of .02 mg. was of interest. Perhaps even more surprising was the fact that no group, not even the control group (group I), experienced weight loss. This could be due either to an attenuation of the culture or to a fair degree of natural resistance in the group of guinea pigs used. In view of the known virulence of H₃₇RV and the fact that the particular strain used was isolated from a guinea pig dead of extensive tuberculosis, it would appear that the latter possibility is the more likely one. Nevertheless, since only two animals (both in group III) showed no disease in lungs, liver, and spleen, since many animals showed widespread disease, and since even the two with uninvolved viscera had infected inguinal nodes, it seems likely that many would eventually have succumbed to tuberculosis had they not been sacrificed. The experiment was terminated after 41 days in order that possible recrudescence of disease in the treated animals after cessation of treatment might not obscure any retardation effected by treatment.

The fact that the animals which received usnic acid (groups II and V) failed to gain weight during the period of treatment to the same extent as the controls and their gain after the end of treatment suggest a toxic action of the mixture of usnic acid and oil-Tween. The amount given was approximately one-third of the lethal dose.

Administration of oil-Tween alone produced no such inhibition of gain in weight. (1).

Gross and microscopic examination of the lungs, livers, and spleens clearly indicates definite retardation of disease in animals treated with 6 mg. of streptomycin per day for 30 days (group III). A similar and quantitatively comparable degree of retardation was achieved by treatment with 2 mg. of streptomycin per day plus usnic acid. On the other hand, there was no evidence that usnic acid alone (group II), in the doses given, affected the course or severity of the disease to any degree. Streptomycin alone in doses of 2 mg. per day (group IV) showed very little retardation of disease. The very definite effect achieved in group V then would seem to indicate a clear potentiating action of usnic acid on streptomycin. Earlier reports of the beneficial action of usnic acid alone were not confirmed in the present series of experiments. Reasons for this are not known although it should be noted that, in the previous experiments, the animals were given a very heavy inoculum intraperitoneally and rapidly developed severe disease. The two experiments are not therefore necessarily comparable.

It has been shown that streptomycin forms a complex with desoxyribonucleic acid (7). However, streptomycin does not interfere with the splitting of desoxyribonucleic acid by desoxyribonuclease (8). Usnic acid, on the other hand, will inactivate desoxyribonuclease although it does not form a complex with desoxyribonucleic acid (8). Thus, both streptomycin and usnic acid may affect the same cellular system (desoxyribonucleic acid-desoxyribonuclease), but in different ways, one acting on the substrate, the other on the enzyme. This observation may account for the synergistic action of the two substances, although the same effect might be obtained if streptomycin and usnic acid each acted on totally different or unrelated systems. We recognize that the system mentioned is not necessarily the one which is significant for the bacteriostatic or bacteriocidal action of either drug, since other systems may be involved.

Although the results obtained show that streptomycin alone in sufficiently large doses is more efficient than usnic acid in arresting tuberculosis in guinea pigs, the observed synergistic action of the two drugs makes it probable that the development of resistance, a serious problem in therapy, may be limited through the combined action of both substances.

The observations presented here may be compared with those obtained with combined streptomycin and PAS therapy (9, 10, 11, 12, 13, 14, 15). The net result of treatment with combined streptomycin and PAS appears to be a summation of the effects obtained with each one. Since no demonstrable retardation of the disease was found with usnic acid alone under the conditions of this experiment,

the observed action of usnic acid and streptomycin would appear to represent potentiation rather than summation.

Summary

Five groups of guinea pigs which had been inoculated with tubercle bacilli were established as follows: I. Untreated; II. Usnic acid only; III. High doses of streptomycin (6 mg./day); IV. Low doses of streptomycin (2 mg./day); V. Usnic acid plus low doses of streptomycin. Severity of tuberculosis was compared among the various groups. Usnic acid alone did not effect any retardation of the disease nor did low doses of streptomycin (2 mg./day). A comparable, marked retardation in the development of the disease was obtained by each of two modes of treatment: (a) with high doses of streptomycin, and (b) with usnic acid combined with low doses of streptomycin.

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Ex-Tuberculosis Patients Show Good Work Records

According to the Bureau of Labor Statistics of the United States Department of Labor, comparison of the work performance records of ex-tuberculous employees with those of unimpaired industrial employees reveals that former tuberculosis patients have fewer disabling injuries and lose less time because of injuries than unimpaired workers; they are also less likely to quit their jobs. In other respects, there is little difference between the records of the two groups.

This study of 513 ex-tuberculous workers and 910 unimpaired employees forms one chapter of a report to the Veterans Administration.¹ An evaluation is made of the efficiency, output, and general desirability as workers of ex-tuberculous persons employed in the industries studied (which represent all groups in the Bureau's Standard Industrial Classification except lumber and timber basic products). The formerly tuberculous employees are compared with a control group of unimpaired workers selected in such a way that each of the ex-tuberculous persons would be matched with at least one unimpaired worker (preferably with two or three) of closely comparable age and experience and the same sex, working on the same job in the same department with similar incentives and hazards. Findings are tabulated on the basis of the various standard work performance criteria (absenteeism, nondisabling and disabling injury experience, output, and quit rate).

Statistical breakdowns show a greater percentage of the 513 arrested cases in the middle age brackets than the 10,515 otherwise impaired workers forming the rest of the survey group.

Ex-tuberculous patients were widely distributed among the various industry classifications. Their jobs required skills ranging from common labor to highly skilled machinist work. Only about 5 per cent, however, were employed on the unskilled jobs. It would appear that job opportunities are greater for those with a skill to sell.

Industrial placement attitudes were found to be generally favorable for former tuberculous patients. Only 7 of the 109 plants studied had exclusion policies affecting such applicants. Reluctance to assign the ex-tuberculous to certain departments in some plants was due to a desire to protect such persons from environmental conditions which might aggravate the impairment; it was not because of a discriminatory employment policy.

It is concluded in the report that the ex-tuberculous employees studied in this survey were "normal workers who, properly placed, were able to compete successfully with unimpaired workers on the same jobs."

¹ U. S. Department of Labor, Bureau of Labor Statistics: *The Performance of Physically Impaired Workers in Manufacturing Industries*. Bulletin No. 923. U. S. Government Printing Office, Washington, 1948. 55 cents. Ch. G, pp. 97-103.

Tuberculosis Facilities and Planning Under the Hospital Survey and Construction Act

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With the enactment on August 13, 1946, of the Hospital Survey and Construction Act (Public Law 725, 79th Cong.), Federal aid to the States and Territories became available for surveys of existing hospital and health-center facilities, for development of programs for the construction of needed facilities and for the construction of public and other nonprofit hospitals in accordance with these State plans.

To date all 48 States, the District of Columbia, and the Territories have surveyed their existing facilities and have prepared plans for hospital construction which have been approved by the Surgeon General. Of the total existing hospital beds reported in the latest approved State plans, about 8 percent, or a total of 93,852 beds, are for the care of the tuberculous; 12,393 or 13 percent of these tuberculosis beds have been declared nonacceptable by the State agencies. (See table 1.)

In determining the total number of tuberculosis beds needed, it is specified in the Hospital Survey and Construction Act that Federal funds may not be used to construct facilities for the tuberculous in excess of a ratio of 2.5 beds per average annual death from tuberculosis in the State during the 5-year period 1940-44. (Averages for more recent 5-year periods may be used providing the rate does not exceed that for 1940-44.) On the basis of this prescribed ratio, a total of 146,926 tuberculosis beds is needed—67,477 beds in addition to the present supply. In other words, only 1.4 acceptable beds per average annual death from tuberculosis are now available in the United States and Territories, or just slightly more than half of the total beds estimated to be needed under the ratio set forth in the Act.

Five States and one Territory, Connecticut, Minnesota, Washington, Wisconsin, North Dakota, and Hawaii, report that they have more than 2.5 beds per tuberculosis death, i. e., more beds than the limit set for Federal aid. Another State, Colorado, has more than 2.5 beds per average annual death but approximately two-thirds of its beds are for the use of out-of-state residents, and additional beds are required for use of State residents. The Virgin Islands reported no acceptable tuberculosis beds, and 9 additional States and Territories have less than one bed per average annual death from tuberculosis, or less than two-fifths of the total tuberculosis beds needed. The following is a

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Table 1. Tuberculosis beds:¹ total existing beds, additional needs and beds being constructed through approved projects Title I, Public Health Service Act²

	Existing beds			Additional beds needed	Beds being constructed in approved tuberculosis projects
	Total	Acceptable	Nonacceptable ³		
United States and Territories.....	93,852	81,459	12,393	67,477	3,091
United States.....	89,392	77,136	12,256	58,867	2,075
Alabama.....	724	519	205	2,939	54
Arizona.....	526	526	1,026
Arkansas.....	1,351	1,351	979
California.....	7,752	5,353	2,399	3,980
Colorado.....	1,270	1,050	220	654
Connecticut.....	1,721	1,721
Delaware.....	193	193	89
Dist. of Columbia.....	1,177	1,052	125	439
Florida.....	1,540	893	647	1,287	400
Georgia.....	1,460	1,460	1,360
Idaho.....	70	70	98
Illinois.....	5,044	5,044	2,167	100
Indiana.....	1,771	1,237	534	1,583
Iowa.....	777	639	138	341
Kansas.....	448	448	562
Kentucky.....	1,640	1,614	26	2,401	64
Louisiana.....	1,286	1,254	32	2,021	100
Maine.....	526	526	211
Maryland.....	1,969	1,829	140	1,206	294
Massachusetts.....	3,695	3,688	7	287
Michigan.....	4,676	3,659	1,017	617	100
Minnesota.....	1,995	1,930	65
Mississippi.....	676	611	65	1,822	154
Missouri.....	1,805	1,805	2,282
Montana.....	235	235	262
Nebraska.....	200	200	303
Nevada.....	21	21	152
New Hampshire.....	189	189	121
New Jersey.....	3,290	3,211	79	461
New Mexico.....	353	353	584
New York.....	12,256	9,540	2,716	4,923
North Carolina.....	2,014	1,830	184	1,660
North Dakota.....	275	275
Ohio.....	3,825	3,332	493	3,771	174
Oklahoma.....	1,264	1,264	1,227	30
Oregon.....	577	495	82	198
Pennsylvania.....	5,671	3,772	1,899	4,948
Rhode Island.....	629	629	84
South Carolina.....	990	794	196	776	194
South Dakota.....	192	192	261
Tennessee.....	1,862	1,862	2,538	300
Texas.....	3,434	3,413	21	5,287	111
Utah.....	96	96	69
Vermont.....	112	112	188
Virginia.....	1,892	1,601	291	1,524
Washington.....	2,394	2,126	268	177
West Virginia.....	1,321	1,021	300	974
Wisconsin.....	2,126	2,019	107
Wyoming.....	82	82	28
Alaska.....	169	169	826
Hawaii.....	1,252	1,137	115	216
Puerto Rico.....	3,017	3,017	7,739	800
Virgin Islands.....	22	22	45

¹ Includes beds in hospitals for the diagnosis and treatment of tuberculosis, excluding preventoria.

² Existing beds and additional needs are based on data reported in latest approved State plans for hospital construction, as of Nov. 30, 1949; data on beds being constructed through approved project applications are as of Oct. 31, 1949. In accordance with the Act, the total number of beds for tuberculosis patients shall not exceed 2.5 times the average annual deaths from tuberculosis in the State over the 5-year period 1940-44, average for other 5-year periods may be used provided the rate does not exceed that for the 1940-44 period.

³ Represents beds classified as "nonacceptable" by the State agencies on the basis of fire hazards, obsolete construction, health hazards, etc.

⁴ This project was initially approved June 10, 1948, when the bed per death ratio was below 2.5.

distribution of the 53 States and Territories by the number of existing acceptable beds per average annual death from tuberculosis:

<i>Number of beds per average annual death from tuberculosis</i>	<i>Number of States and Territories</i>
0	1
0.01-0.49	2
0.50-0.99	8
1.00-1.49	21
1.50-1.99	11
2.00-2.49	3
2.50 and over	7
	53

Thus far, construction of tuberculosis facilities under the program has not kept pace with the construction of general and specialized hospital beds. Whereas the need for additional general and specialized hospital beds is only four times that for additional tuberculosis beds (see table 2), approved projects for new construction in general and specialized hospitals contain about 12 times as many beds as do approved projects for tuberculosis hospitals. Moreover, only 27, or 3.2 percent of the 836 approved project applications for all types of hospitals have been for tuberculosis projects. In other words, approved construction projects for tuberculosis hospital beds are meeting requirements at a much slower rate than are projects for general hospitals.

If we compare the current supply of acceptable beds with total requirements (chart), it becomes apparent that there is a slightly greater proportionate need for additional tuberculosis hospital construction at this time than for general and specialized beds (46 percent against 36 percent, respectively). Assuming that construction funds should be used for specific facilities in proportion to the relative need for those facilities, it is apparent that the amounts of Federal funds used by the States for tuberculosis hospitals were disproportionately

Table 2. Tuberculosis, general, and special¹ hospital facilities: comparison of beds available, beds needed, and new construction under the Hospital Survey and Construction Act, United States and Territories as of Oct. 31, 1949

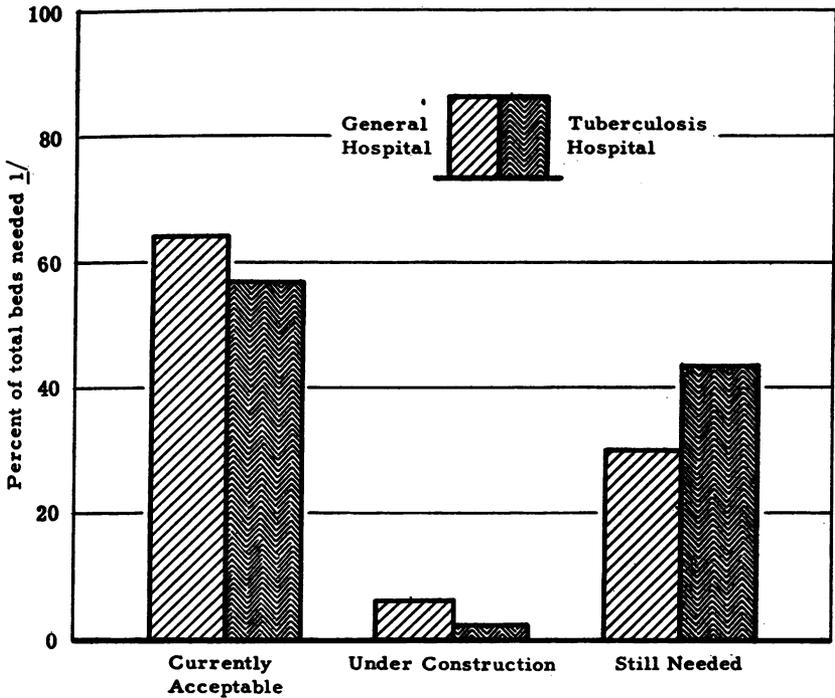
	Number of beds		Percent of total beds needed	
	General and special hospitals	Tuberculosis hospitals	General and special hospitals	Tuberculosis hospitals
Total bed requirements ²	680,884	146,926	100	100
Existing acceptable beds	434,882	81,459	64	55
Additional beds needed	246,002	67,477	36	46
Beds approved for construction ³	37,687	3,091	6	2

¹ General and special hospital facilities include hospitals planned for the care and treatment of acute conditions and specialized types of cases other than mental and tuberculosis, and chronic disease.

² Total beds needed to provide adequate hospital facilities is defined in the act as 4.5 to 5.5 beds per 1,000 population (depending on population density) for general hospital beds and not more than 2.5 beds per average annual death from tuberculosis for tuberculosis hospital beds.

³ 15 percent of the additional beds needed for general hospitals and only 4 percent of the additional beds needed for tuberculosis hospitals have been approved for construction.

**PROGRESS IN MEETING THE NEED FOR ADDITIONAL BEDS UNDER
THE HOSPITAL SURVEY AND CONSTRUCTION ACT
(General Hospitals Compared with Tuberculosis Hospitals)**



^{1/} Under the Hospital Survey and Construction Act total beds needed for tuberculosis is defined as not more than 2½ beds per average annual tuberculosis death in the period 1940-1944, and for general hospital beds as not more than 4½ beds per 1000 population.

low, since only \$8,883,765 were used for tuberculosis hospitals, as compared with \$160,079,404 for general hospital projects (as of October 31, 1949).

On October 25, 1949, several amendments to the Act were passed which vastly liberalize the original provisions. These amendments, which are contained in Public Law 380, incorporate the following:

1. The duration of the program is extended for an additional 4 years, i. e., from 1951 to 1955.

2. The annual Federal allotments to the States are increased from \$75,000,000 to \$150,000,000. In general, each State's allotment will be doubled.

3. Formerly the Federal Government would bear one-third of the cost of construction of aided projects. Now each State will have considerable discretion in determining the proportion of the cost of hospital and health center projects to be met from Federal funds. The State has two basic alternatives: the State may determine that the

Federal share shall be a uniform percentage for all projects within the State. In this case, it may set the Federal share at a figure between a floor of 33½ percent and a ceiling which varies from State to State, being 33½ percent in the States with the highest per capita income, and 66½ percent in the States with the lowest per capita income. For example, this ceiling for Minnesota is 56 percent. Minnesota could set the Federal share at any figure between 33½ and 56 percent.

Or the State may decide to vary the Federal share among projects or classes of projects in accordance with the economic resources of local areas or other equitable factors. If it decides to do this it may vary the Federal share within a range of 33½ percent to 66½ percent, i. e., it could decide that Federal funds would pay one-third of the cost of a hospital in a wealthy area, and as high as two-thirds in a poor area.

4. Special aid is provided in so called hardship cases, i. e., hospitals that were started without Federal aid, and cannot be completed without such aid.

5. Annual appropriations of up to \$1,200,000 are authorized for grants for research and demonstration projects relating to the development, utilization, and coordination of hospital services, facilities, and resources. Such grants may be made to public or nonprofit organizations. The principal objective of this provision is to stimulate coordination of hospital services on a regional basis.

As has been demonstrated, there has been very little new construction of tuberculosis beds under the Act.

There is, it is true, some construction of beds for the tuberculous outside the Hospital Survey and Construction Act. Nevertheless, the need for such facilities remains acute in virtually every State of the Nation. Today, only six States and one Territory meet the recommended ratio of 2½ tuberculosis beds per average annual death from the disease.

In many communities, tuberculosis control workers are daily confronted by the problem of long waiting lists for admission to tuberculosis hospitals. Despite the obvious public health hazards, patients are frequently and of necessity permitted to remain in contact with members of their families and their communities, and necessary treatment is indefinitely postponed.

At times this intolerable situation has forced the adoption of unrealistic admission and discharge policies, to the general detriment of the public health program. In some areas, policies limiting admissions to sputum-positive or far advanced cases, for example, have grown to be matters of very real concern to local tuberculosis control workers. In others, regulations restricting a patient's hospital residence to a certain period of time—usually far less than necessary—contain grave implications for the future control of the disease wherever they are invoked.

Public health officers, public health nurses, and all other professional workers concerned with tuberculosis control in local areas repeatedly emphasize the hardships resulting from the extreme shortage of tuberculosis hospitalization facilities. Today case finding, although valuable because it identifies cases and puts them under medical supervision, does not achieve maximum benefits when those who need hospitalization cannot receive it.

At this time, any attempt to analyze the reasons for the relative lack of activity in tuberculosis hospital construction would be based on conjecture. Until now, the emphasis has been upon the construction of general hospitals, and the highest priorities have been given, and are still going to this type of construction.

To be sure, the need for general hospital beds, by sheer weight of numbers, is indeed great, so that the emphasis has not been misdirected. However, it is possible that this very emphasis has generated a misapprehension among tuberculosis control officials that the provisions of the Act do not apply to tuberculosis. Such is not at all the case, nor was it ever so intended.

The Act applies with equal force to the construction of tuberculosis facilities where the need can be demonstrated, and, as is evident from the earlier sections of this paper, the need can indeed be demonstrated in most areas of the country.

The Act, as now amended, provides an excellent opportunity for material advances in tuberculosis control everywhere. Liberal financial assistance is now available to the States in meeting the most costly phase of tuberculosis control—that of hospital care for all requiring it. Public health workers should therefore take every opportunity to make local tuberculosis hospitalization needs known to State hospital planning boards and to the members of their communities from whom major support must ultimately derive.

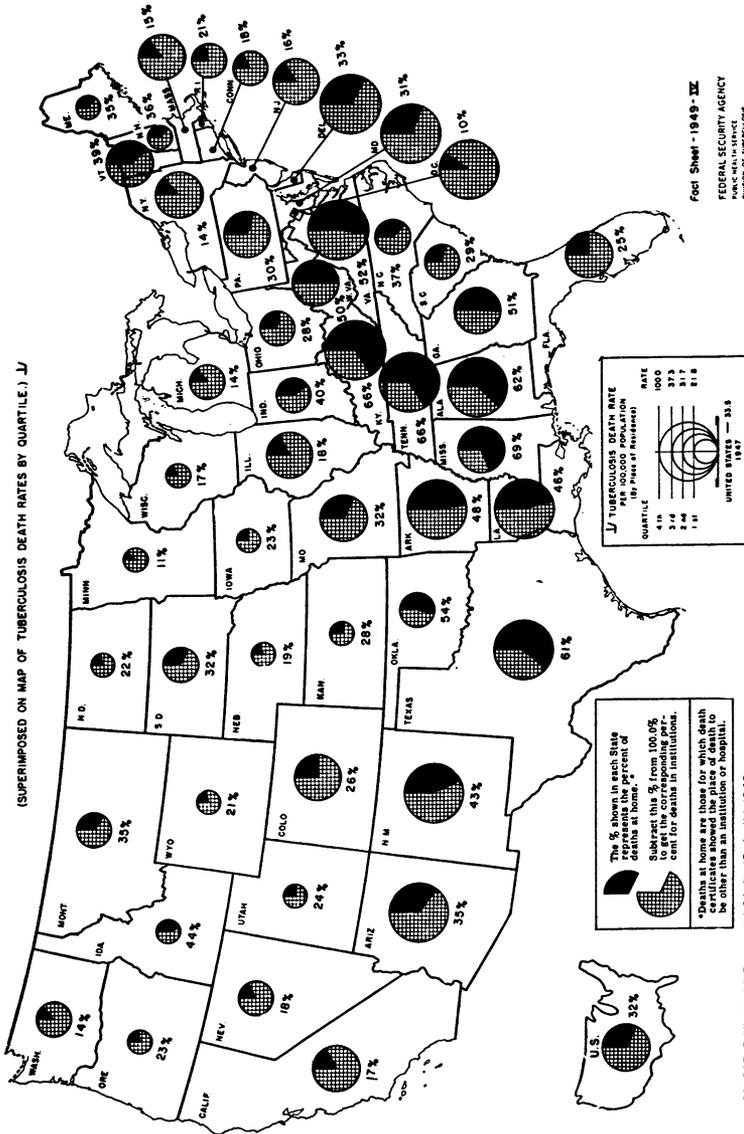
Finally, serious consideration should be given to integrating plans for tuberculosis bed construction with those of general hospitals. Past experience has shown this to be a highly desirable practice, and several States, including New Hampshire, California, Colorado, and Kentucky, have already incorporated it in their plans for future hospital construction. In some areas, in fact, this trend toward the incorporation of tuberculosis treatment units within general hospitals has become quite marked. This is especially true of rural areas seeking a practical answer to the problem of inadequate tuberculosis hospital care facilities.

The means and the techniques for reducing the shortage of tuberculosis hospital beds are now more readily available than ever before. Aggressive action on the part of local public health officials and tuberculosis control workers is what is now needed to bring the nationwide program of effective tuberculosis hospitalization to fruition.



**RESPIRATORY TUBERCULOSIS DEATHS AT HOME AND IN INSTITUTIONS
FOR EACH STATE AND THE UNITED STATES, 1947**

(SUPERIMPOSED ON MAP OF TUBERCULOSIS DEATH RATES BY QUARTILE.)



The % shown in each State represents the percent of deaths at home. To get the corresponding percent for deaths in institutions, subtract the % shown from 100.0%.

States in which the percent for deaths in institutions is other than an institution or hospital.

Fact Sheet - 1949 - III
FEDERAL SECURITY AGENCY
U.S. GOVERNMENT PRINTING OFFICE

SOURCE: Public Health Reports, Vol. 64, No. 13, April 1, 1949

INCIDENCE OF DISEASE

No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring

UNITED STATES

REPORTS FROM STATES FOR WEEK ENDED JANUARY 14, 1950

For the current week, increases in reported cases of measles (from 3,044 to 4,946), whooping cough (from 1,660 to 2,159), influenza (from 4,077 to 4,325), and scarlet fever (from 1,232 to 1,425) were shown over the preceding week. Additional diseases showing increases for the current period are diphtheria, meningococcal meningitis, all forms of pneumonia, Rocky Mountain spotted fever, tularemia, and typhoid and paratyphoid fever.

Although reported incidence of measles increased sharply for the week, the total remained below the 5-year (1945-49) median for the corresponding week. The current cumulative totals for the calendar and seasonal years are also below the corresponding medians for the same periods. Michigan reported the largest numerical increase in measles, from 167 to 1,336, for the current week. The 5-year (1945-49) median for the week is 310. Other States showing increases in reported cases of measles are California (from 13 to 187), New Jersey (from 398 to 528), Wisconsin (from 99 to 233), and New Mexico (from 4 to 102).

Reported cases of influenza increased chiefly in Texas (from 2,432 to 2,667), Georgia (from 202 to 314), Oklahoma (from 90 to 163), and Nebraska (from 11 to 42). Virginia reported a decrease of 124 cases of influenza for the week, from 513 to 389.

Michigan reported the largest increase (from 42 to 148) in cases of scarlet fever for the week. The 5-year (1945-49) median for the week for Michigan is 136.

Reported incidence of other diseases increased as shown in the following table:

	<i>Current week</i>	<i>Last week</i>	<i>1945-49 median</i>
Diphtheria.....	205	166	340
Meningitis, meningococcal.....	94	73	100
Pneumonia.....	2,262	2,210	-----
Rocky Mountain spotted fever.....	3	1	0
Tularemia.....	23	21	43
Typhoid and paratyphoid.....	38	24	41
Whooping cough.....	2,159	1,660	2,263

One case of anthrax was reported in Arkansas, and one case of smallpox was reported in Kentucky.

Telegraphic case reports from State health officers for week ended January 14, 1950

[Leaders indicate that no cases were reported]

Division and State	Diphtheria	Encephalitis, infectious	Influenza	Measles	Menigitis, meningococcal	Pneumonia	Poliomyelitis	Rocky Mountain spotted	Scarlet fever	Smallpox	Tularemia	Typhoid and paratyphoid fever	Whooping cough	Rebels in animals
NEW ENGLAND														
Maine.....				43		16	1		16			2	16	
New Hampshire.....						1			1					
Vermont.....									9				26	
Massachusetts.....				26	1		1		86				107	
Rhode Island.....	1		1	2			2		12				4	
Connecticut.....	1			24		51	1		21				105	
MIDDLE ATLANTIC														
New York.....	15		11	258	5	268	9		82				264	12
New Jersey.....			4	528	4	141	6	1	34				182	1
Pennsylvania.....	2			96	7	110	5		83		1		176	1
EAST NORTH CENTRAL														
Ohio.....	14			94	5	84	2	1	182			1	134	9
Indiana.....	4		5	28	2	22	2		53			1	18	315
Illinois.....	3		3	69	4	62	4		48			1	67	2
Michigan.....	7	3		1,386	5	56	4		148		8		241	1
Wisconsin.....			14	233	2	17			60				122	
WEST NORTH CENTRAL														
Minnesota.....	10			82	3	5	3		15				21	
Iowa.....				162	2	3	6		8				13	
Missouri.....	2				4	8	2		12		2	1	16	
North Dakota.....				4										1
South Dakota.....	2								3			1	1	
Nebraska.....	1		42	194		3	1		17			1	4	
Kansas.....	2	2	1	5		7			20				8	1
SOUTH ATLANTIC														
Delaware.....	1			24					4				2	
Maryland.....	3	1	2	50	2	63	1		15			3	74	
District of Columbia.....				35		13			3					
Virginia.....	8		389	35	3	96	4		35			5	16	1
West Virginia.....			49	29	3	29	2		13				60	4
North Carolina.....	10			169	2		2		61		1		34	
South Carolina.....	3		19	147		26			3			1	3	13
Georgia.....	9		314	16	1	22	1		19		1		8	16
Florida.....	4	4	11	24	6	26	4		4			2	2	2

EAST SOUTH CENTRAL									
Kentucky.....	5	36	8	1	37	1	3	16	8
Tennessee.....	5	119	4	1	88	1	1	56	7
Alabama.....	5	178	1	1	80	1	1	63	8
Mississippi.....	10	21	3	2	32	2	2	5	8
WEST SOUTH CENTRAL					9			4	1
Arkansas.....	3	6	2	1	3	3	4	5	3
Louisiana.....	2	25	2	2	1	2	4	2	1
Oklahoma.....	4	6	2	2	8	2	2	13	2
Texas.....	40	63	5	10	34	1	1	84	17
MOUNTAIN									
Montana.....	1	120	1	5	10	10	1	4	
Idaho.....	1	3	1	1	5	5	1	1	
Wyoming.....	2	5	1	1	3	3	1	1	
Colorado.....	2	80	2	2	16	16	1	14	
New Mexico.....	5	3	3	2	6	6	1	8	
Arizona.....	5	102	3	2	7	7	1	8	
Utah.....	2	188	3	4	1	1	3	49	
Nevada.....	1	119	3	4	7	7	3	10	
PACIFIC									
Washington.....	2	61	1	2	37	37	32	32	
Oregon.....	1	43	2	5	14	14	18	18	
California.....	11	187	7	17	79	79	3	118	
Total.....	205	4,325	94	123	1,425	1,425	27	2,169	128
Median, 1945-49.....	340	4,728	100	64	2,467	2,467	43	2,263	
Year to date 2 weeks.....	371	7,990	167	247	2,657	2,657	48	3,819	248
Median, 1945-59.....	706	8,083	183	111	4,474	4,474	82	4,097	
Seasonal low week ends.....	(27th)	(30th)	(37th)	(11th)	(32d)	(35th)	(11th)	(9th)	
Since seasonal low week.....	July 9	July 30	Sept. 3	Mar. 19	Aug. 13	Sept. 3	Mar. 19	Oct. 1	
Median, 1944-45 to 1948-49.....	4,642	27,120	1,080	41,707	19,086	2,499	2,499	24,365	
	8,272	34,207	1,155	19,083	31,102	3,609	3,609	28,434	

1 New York City only.
 2 Including streptococcal sore throat.
 3 Two weeks report.
 Anthrax: Arkansas, 1 case.
 Alaska: Pneumonia 1.
 Hawaii: Influenza 783, measles 1, meningitis meningococcal 1.

TERRITORIES AND POSSESSIONS

Hawaii Territory

Plague (rodent).—Under date of January 11, 1950, plague infection was reported proved in one rat found dead on December 13, 1949, in Kapulena Area, Hamakua District, Island of Hawaii, T. H.

Panama Canal Zone

Notifiable diseases—November 1949.—During the month of November 1949, certain notifiable diseases were reported in the Panama Canal Zone and terminal cities as follows:

Disease	Residence ¹									
	Panama City		Colon		Canal Zone		Outside the zone and terminal cities		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Chickenpox.....	2		7		7				16	
Diphtheria.....	2		1				2		5	
Dysentery:										
Amebic.....	1		2		1		3		7	
Bacillary.....	2						1		3	
Hepatitis, infectious.....	1				1				2	
Malaria ²	2				5		29		36	
Measles.....					8				8	
Mumps.....	2				20				22	
Pneumonia.....		3		2	34	4		6	34	15
Tetanus.....	1								1	
Tuberculosis.....		23		6	1			10	1	39
Typhoid fever.....			1				2		3	
Whooping cough.....				1	6			1	3	2
Yaws.....	1						1		2	

¹ If place of infection is known, cases are so listed instead of by residence.

² Two recurrent cases.

³ Reported in the Canal Zone only.

Puerto Rico

Notifiable diseases.—4 weeks ended November 26, 1949, and 5 weeks ended December 31, 1949.—During the 4 weeks ended November 26, 1949, and 5 weeks ended December 31, 1949, cases of certain notifiable diseases were reported in Puerto Rico as follows:

Disease	Cases		Disease	Cases	
	4 weeks ended Nov. 26, 1949	5 weeks ended Dec. 31, 1949		4 weeks ended Nov. 26, 1949	5 weeks ended Dec. 31, 1949
Chickenpox.....	8	4	Syphilis.....	23	44
Diphtheria.....	37	46	Tetanus.....	6	12
Dysentery.....	1		Tetanus, infantile.....	2	3
Gonorrhoea.....	62	130	Tuberculosis (all forms).....	495	938
Influenza.....	1,404	369	Typhoid fever.....	3	2
Malaria.....	11	10	Typhus fever (murine).....	1	
Measles.....		2	Whooping cough.....	255	191
Poliomyelitis.....	5	2			

FOREIGN REPORTS

CANADA

Provinces.—Notifiable diseases—Week ended December 24, 1949.—
 During the week ended December 24, 1949, cases of certain notifiable diseases were reported by the Dominion Bureau of Statistics as follows:

Disease	New-found-land	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alber-ta	British Colum-bia	Total
Chickenpox.....	1		8		254	335	35	53	75	51	812
Diphtheria.....					7	5					12
Dysentery:											
Amebic.....							2	1			1
Bacillary.....										1	3
Encephalitis, in-fectious.....						1	2				2
German measles.....			1		2	37	1	10	92	32	176
Influenza.....			6				1				7
Measles.....			2		179	87	26	83	90	290	757
Meningitis, men-ingococcal.....					1						1
Mumps.....			35		134	269	2	8	51	92	591
Poliomyelitis.....						1					1
Scarlet fever.....	9			1	43	39	5	1	50	8	156
Tuberculosis (all forms).....	9		17	2	122	22	10	12	29	26	249
Typhoid and para-typhoid fever.....					7	1					8
Undulant fever.....					1	1		2		2	6
Veneral diseases:											
Gonorrhea.....	5		6	8	74	57	21	14	24	89	298
Syphilis.....			4	4	45	15	6	25	1	18	118
Other forms.....										1	1
Whooping cough.....			2		170	32				4	208

CUBA

Habana—Notifiable diseases—4 weeks ended November 26, 1949.—
 During the 4 weeks ended November 26, 1949, certain notifiable diseases were reported in Habana, Cuba, as follows:

Disease	Cases	Deaths	Disease	Cases	Deaths
Diphtheria.....	21	2	Rickettsiosis.....	1	
Leptospirosis.....	1		Tuberculosis.....	2	1
Malaria.....	1		Typhoid fever.....	1	
Measles.....	3				

Provinces—Notifiable diseases.—4 weeks ended November 26, 1949.—
 During the 4 weeks ended November 26, 1949, cases of certain notifiable diseases were reported in the Provinces of Cuba as follows:

February 3, 1950

CUBA—Continued

Disease	Pinar del Rio	Habana ¹	Matanzas	Santa Clara	Camaguey	Oriente	Total
Cancer	8	9	12	22	1	16	68
Chickenpox						1	1
Diphtheria	4	26	6	1			37
Leprosy		3					4
Leptospirosis		1					1
Malaria	1	1		1	2	22	27
Measles		3					4
Polomyelitis					1		1
Rickettsiosis		1					1
Tuberculosis		12	10	26	10	10	68
Typhoid fever	9	6	4	1	1	34	55
Undulant fever				1			1
Yaws						5	5

¹ Includes the city of Habana.

Ethiopia

Malaria.—Information dated January 7, 1950, states that a serious epidemic of pernicious malaria has been reported near Dessie in Wollo Province, Ethiopia. It is said that 582 deaths from this disease occurred in the small town of Komblochia during the months of September and October 1949, and an estimated number of 500–600 deaths were reported in adjacent areas during the same period.

Madagascar

Notifiable diseases—November 1949.—Notifiable diseases were reported in Madagascar and Comoro Islands during November 1949, as follows:

Disease	Aliens		Natives	
	Cases	Deaths	Cases	Deaths
Beriberi			2	
Bilharziasis			53	
Cerebrospinal meningitis			12	4
Diphtheria			1	1
Dysentery, amebic	10		406	8
Erysipelas			17	
Influenza	93		4,841	43
Leprosy			40	
Malaria	347		33,067	224
Measles	1		322	7
Mumps	3		290	
Plague			13	11
Pneumonia, broncho	3		455	57
Pneumonia, pneumococcic	4		368	46
Puerperal infection	2		1	
Relapsing fever	2		1	
Tuberculosis, pulmonary	3		90	15
Typhoid fever	2	1	12	1
Whooping cough	4		392	19

REPORTS OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER RECEIVED DURING THE CURRENT WEEK

Note.—The following reports include only items of unusual incidence or of special interest and the occurrence of these diseases, except yellow fever, in localities which had not recently reported cases. All reports of yellow fever are published currently.

A table showing the accumulated figures for these diseases for the year to date is published in the PUBLIC HEALTH REPORTS for the last Friday in each month.

Plague

India—Central Province.—During the week ended December 3, 1949, 777 cases of plague, with 99 deaths, were reported in Central Province, India.

Netherlands Indies—Java—Jogjakarta.—For the week ended January 7, 1950, 17 fatal cases of plague were reported in Jogjakarta City, Java.

Siam (Thailand).—During the week ended December 24, 1949, 4 cases of plague (2 fatal) were reported in Siam—2 cases, 1 death, in Phitsnulok Province, 2 cases, 1 death, in Ubonratchthani Province.

Smallpox

Arabia—Jedda and Mecca.—During the week ended December 31, 1949, 96 cases of smallpox were reported in Jedda, Arabia, and 19 cases in Mecca.

Burma—Bassein and Rangoon.—During the month of December 1949, 143 cases of smallpox were reported in Bassein and 85 cases in Rangoon, Burma. For the week ended January 7, 1950, 26 cases were reported in Bassein, and 42 cases in Rangoon.

Indochina (French)—Tonkin.—During the week ended December 31, 1949, 109 cases of smallpox were reported in Laokay Province, Tonkin State, French Indochina.

Mexico.—During the period January 1–June 30, 1949, 677 cases of smallpox, with 226 deaths, were reported in Mexico. For the same period in 1948, 1,029 cases, with 623 deaths, were reported in that country.

Niger Territory.—For the period December 11–20, 1949, 80 cases of smallpox were reported in Niger Territory, French West Africa.

Pakistan—Chittagong.—For the week ended January 7, 1950, 18 cases of smallpox were reported in Chittagong, Pakistan.

Syria—Tartus.—During the week ended December 17, 1949, 4 cases of smallpox were reported in the port of Tartus, Syria.

Typhus Fever

British East Africa—Tanganyika—Dar-es-Salaam.—During the week ended December 10, 1949, 1 case of typhus fever was reported in Dar-es-Salaam, Tanganyika Territory, British East Africa.

China.—Typhus fever has been reported in cities in China as follows: November 21–30, 1949, Canton 1 case; December 1–10, 1949, Tientsin 1 case; week ended December 31, 1949, Shanghai, 1 case.

Pakistan—North West Frontier Province.—During the week ended December 31, 1949, 25 cases of typhus fever, with 11 deaths, were reported in North West Frontier Province, Pakistan.

DEATHS DURING WEEK ENDED JAN. 14, 1950

	Week ended Jan. 14, 1950	Correspond- ing week, 1949
Data for 94 large cities of the United States:		
Total deaths.....	9,906	9,896
Median for 3 prior years.....	10,013	-----
Total deaths, first 2 weeks of year.....	19,619	20,686
Deaths under 1 year of age.....	605	716
Median for 3 prior years.....	716	-----
Deaths under 1 year of age, first 2 weeks of year.....	1,254	1,425
Data from industrial insurance companies:		
Policies in force.....	64,757,993	65,790,577
Number of death claims.....	12,525	12,566
Death claims per 1,000 policies in force, annual rate.....	10.1	10.0
Death claims per 1,000 policies, first 2 weeks of year, annual rate.....	9.5	9.7